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EXPERIMENTAL STUDIES

Prostaglandin E_1 Coronary Venous Retroperfusion in Acute Myocardial Ischemia: Effects on Regional Left Ventricular Function and Infarct Size

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Prostaglandin E_1 was administered by means of coronary venous synchronized retroperfusion and the effectiveness of the combined (prostaglandin-retroperfusion) system was examined during acute myocardial ischemia in 10 closed chest anesthetized dogs. Such treatment was administered between 30 minutes and 3 hours after occlusion of the proximal left anterior descending coronary artery. An equivalent series of 10 dogs with arterial blood retroperfusion alone and 9 untreated dogs served as control subjects. Standardized two-dimensional echocardiographic measurements of global and regional left ventricular function were performed in five short-axis cross sections. The global low left ventricular section and its profoundly ischemic anterolateral region exhibited distinctly improved systolic fractional area changes as a result of the prostaglandin E_1 retroperfusion treatment between 30 minutes and 3 hours after occlusion (22.9 ± 1.5 to 41.2 ± 4.0% and 1.8 ± 3.6 to 29.4 ± 5.6%, respectively). In contrast, further deterioration in function was noted during an untreated equivalent coronary occlusion period (16.3 ± 2.7 to 10.0 ± 3.3% and 12.6 ± 6.1 to 4.1 ± 6.9%). Although arterial blood retroperfusion alone provided distinct benefits in the ischemic region of a midpapillary echo section (from 13.4 ± 3.9 to 32.1 ± 10.4%, $p < 0.05$), no improvements were observed in profoundly jeopardized segments at the low left ventricular level (5.6 ± 6.0 to 0.9 ± 5.7%).

Triphenyltetrazolium chloride delineation of infarction revealed significant myocardial salvage with prostaglandin E_1 retroperfusion as compared with findings in untreated control dogs (3.7% ± 1.3% of the left ventricle versus 9.3 ± 1.9%, $p < 0.05$). The respective ratios of necrosis to glycogen-depleted ischemic zones in a mid-left ventricular slab were 19.5 ± 6.4% versus 47.1 ± 8.9 ($p < 0.05$).

It is concluded that retrograde prostaglandin E_1 administration may further enhance the effectiveness of synchronized coronary venous retroperfusion treatment of jeopardized acutely ischemic myocardium.

Prostaglandin E_1 has been reported to provide direct myocardial benefits in acute ischemia, by virtue of coronary vasodilation along with possibly enhanced myocardial contractility and counteraction on platelet aggregation (1–4). Synchronized coronary venous retroperfusion provides an alternative route to delivery of arterial blood or pharmacologic agents to otherwise poorly accessible zones distal to a coronary occlusion (5–12). The current experimental study examined the effectiveness of administering prostaglandin E_1 by synchronized retroperfusion as a means for treatment of profoundly jeopardized ischemic myocardium after acute coronary artery occlusions.

Methods

Experimental preparation. Twenty-nine adult dogs weighing 20 to 30 kg were premedicated with morphine sulfate (1.5 mg/kg intramuscularly), followed by sodium

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JACC Vol. 3, No. 4
April 1984:939–47

pentobarbital anesthesia (25 mg/kg intravenously). After endotracheal intubation, ventilation was maintained with a respirator (Harvard Apparatus Co.) using a mixture of 95% oxygen and 5% carbon dioxide. Heparin (10,000 IU, intravenously) was given prior to instrumentation and then supplemented (3,000 IU) every 2 hours. A continuous intravenous infusion of physiologic saline solution was maintained at a rate of 100 to 120 cc/min throughout the experiments. Under fluoroscopic control, catheters were placed into the ascending aorta, left ventricle and pulmonary artery. After selective coronary angiography, a balloon-tipped catheter was positioned in the proximal left anterior descending coronary artery as described previously (13). A special retroperfusion autoinflatable balloon catheter was inserted under fluoroscopic control into the great cardiac vein through the left internal jugular vein (6).

Aortic and left ventricular blood pressure tracings (with magnified left ventricular end-diastolic pressure) were obtained using Statham P23Db transducers and monitored on a physiologic recorder (model VR12, Electronics for Medicine). The first derivative of left ventricular pressure (dP/dt) was derived by electrical differentiation. Cardiac output was determined using the thermodilution method (Cardiac Output Computer model 9520, American Edwards Laboratories), and cardiac index and systemic vascular resistance were calculated. Electrocardiograms were also monitored on a V_4 equivalent lead. Arterial blood was sampled for routine blood gas determinations.

Regional left ventricular wall motion studies. Two-dimensional echocardiography (ATL Mark III) was employed for sequential quantitative evaluation of left ventricular function using the approach described by Wyatt et al. (14). Images of five short-axis as well as long-axis left ventricular cross sections were obtained in each dog. Standardized computer-aided subdivision of each of the short-axis cross sections into eight equal segments and analysis of segmental endocardial wall motion were based on a fixed referencing system using the endocardial geometric center of the section (15). Sectional and segmental systolic fractional area changes were used as indexes of contractile function.

Detailed echographic study in ischemic and remote zones concentrated on the short-axis cross section at a low left ventricular level (near the apex) which generally exhibits profound ischemic injury after acute proximal left anterior descending coronary artery occlusion, and which is also most difficult to treat with interventions. On the basis of prior investigations, segments with an abnormal fractional area change of less than 20% at 30 minutes after the coronary occlusion were considered ischemic, and their average change from the control period was also studied and at 3 hours after occlusion. Usually, fractional area changes were less than 20% in two to four octants in each short-axis section. The systolic fractional area change of two segments most remote from the ischemic region was averaged to characterize contraction of the nonischemic myocardium. Left ventricular volumes and ejection fraction were reconstructed as previously described (14).

Pathologic study. After the study was completed, each dog heart was excised and cut into transverse 1 cm thick slices, parallel to the atrioventricular (AV) groove. Alternate slices were then incubated in triphenyltetrazolium chloride (16) or fixed in Carnoy's solution, which preserves tissue glycogen. Study of adjacent surfaces of triphenyltetrazolium chloride-stained slices and periodic acid-Schiff (PAS)-stained giant histologic sections of Carnoy's fixed tissue provided comparison of areas of necrosis and ischemia at different levels of the ventricle. Infarct size and extent of the ischemic zone in giant histologic sections were measured by planimetry (16).

Synchronized retroperfusion system. The synchronized retroperfusion system (Fig. 1) was used to deliver arterial blood alone or with prostaglandin E_1 into regional coronary veins. The arterial blood was shunted from the

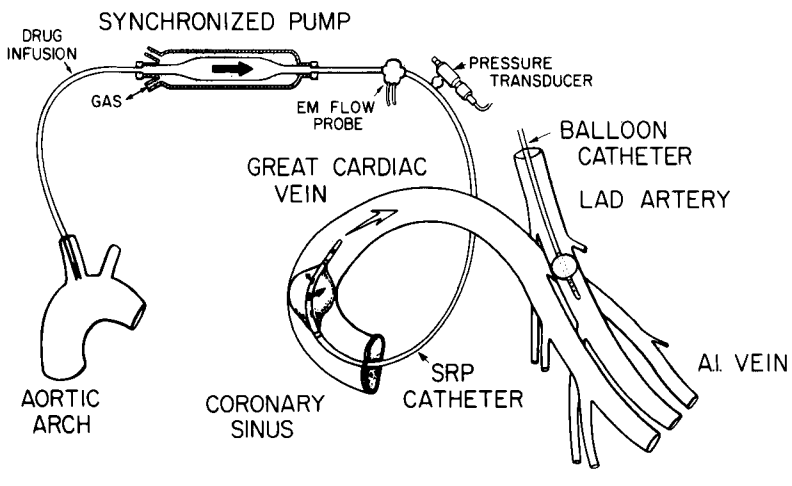

Figure 1. Schematic diagram of the experimental synchronized retroperfusion system. Arterial blood is shunted from the brachial artery into the great cardiac vein and regional anterior interventricular (A.I.) coronary vein that adjoin the left anterior descending (LAD) coronary artery. The latter is occluded by means of an intracoronary balloon catheter to create a zone of acute ischemia to be treated by retroperfusion. Arterial blood is pumped by means of an electrocardiographic synchronized gas-actuated bladder pump that propels blood in retrograde manner during diastole through a special autoinflatable balloon catheter (SRP) into the coronary vein. The retroperfusion flow rate is monitored by means of an electromagnetic flowmeter (EM FLOW) probe. The site of infusion of prostaglandin E_1 is also shown.

Table 1. Hemodynamic Values During 3 Hours of Left Anterior Descending Coronary Artery Occlusion in Three Groups of Closed Chest Dogs

	HR	SBP	LVEDP	dP/dt max	CI	SVR
Preocclusion						
Group A	81 ± 5	120 ± 4	4.3 ± 0.9	1433 ± 96	2.84 ± 0.19	2561 ± 222
Group B	81 ± 6	126 ± 6	3.2 ± 0.6	1672 ± 138	2.97 ± 0.26	2735 ± 367
Group C	102 ± 8	112 ± 5	8.6 ± 0.8	1671 ± 172	2.79 ± 0.47	2667 ± 290
30 minutes' occlusion						
Group A	98 ± 4*	118 ± 4	10.9 ± 1.9*	1227 ± 58*	2.26 ± 0.12*	3157 ± 290*
Group B	91 ± 8	126 ± 4	7.9 ± 1.3*	1564 ± 83	2.45 ± 0.26*	2870 ± 263
Group C	109 ± 7	114 ± 5	14.6 ± 1.6*	1296 ± 169*	2.35 ± 0.23*	3203 ± 337*
3 hours' occlusion						
Group A	124 ± 5*†	111 ± 3	0.85 ± 0.9*†	1449 ± 79†	2.30 ± 0.24*	4226 ± 346*†
Group B	126 ± 4*†	123 ± 3	0.92 ± 0.5*†	1597 ± 94	2.03 ± 0.13*†	3636 ± 262*†
Group C	125 ± 9*†	118 ± 3	15.3 ± 2.1*	1238 ± 203*	1.78 ± 0.09*†	4226 ± 346*†

Values are mean values ± standard error of the mean. *,† $p < 0.05$ (* versus preocclusion, † versus 30 minutes of occlusion). CI = cardiac index (liters/min per m^2); dP/dt max = maximal rate of rise of left ventricular pressure (mm Hg/s); Group A = dogs with prostaglandin E_1 administration and synchronized retroperfusion (both initiated after measurements obtained 30 minutes after coronary occlusion); group B = dogs with retroperfusion alone; group C = untreated dogs with 3 hours of occlusion; HR = heart rate (beats/min); LVEDP = left ventricular end-diastolic pressure (mm Hg); SBP = systolic blood pressure (mm Hg); SVR = systemic vascular resistance (dynes·s·cm^{-5}).

brachial artery into a gas-actuated bladder pump triggered by the electrocardiogram, and was delivered during diastole, via a special retroperfusion catheter placed within the great cardiac vein, to the myocardial zone subserved by the left anterior descending coronary artery. The diastolic flow induces autoinflation of the balloon near the tip of the retroperfusion catheter, causing a brief obstruction of the great cardiac vein, thus propelling arterial blood unidirectionally toward the anterior intraventricular veins. During systole retroperfusion flow was stopped by the synchronized pump, causing collapse of the catheter balloon and facilitating drainage of coronary venous blood through the coronary sinus into the right atrium. The pumping system was controlled to limit retroperfusion flow rates within a range of 40 to 70 cc/min, as measured by an electromagnetic flowmeter (model ABC 10008 Omnicraft).

Experimental protocol. The animal preparation was stabilized and the experiment started approximately 30 minutes after completion of instrumentation. The coronary artery was occluded by inflation of the intracoronary balloon positioned immediately distal to the first diagonal branch of the left anterior descending coronary artery. Twenty-nine dogs that survived the first 30 minutes of coronary occlusion were used for study of either prostaglandin E_1 (group A, 10 dogs), retroperfusion alone (group B, 10 dogs) or no treatment (group C, 9 dogs). Several other dogs developed ventricular fibrillation within the first 30 minutes after coronary occlusion and were, therefore, excluded from the study. There were no deaths between 30 minutes and 3 hours of coronary occlusion in any of the groups.

Table 2. Two-Dimensional Echocardiographic-Derived Systolic Fractional Area Changes (FAC [%]) in Low Left Ventricular Short-Axis Section

		Segmental FAC (%)	
	Sectional FAC (%)	Ischemic Zone	Remote Zone
Preocclusion			
Group A	57.1 ± 1.6	53.0 ± 2.4	61.4 ± 3.4
Group B	57.2 ± 1.9	53.3 ± 4.1	60.3 ± 2.0
Group C	55.4 ± 1.1	54.3 ± 2.3	52.3 ± 4.1
30 minutes' occlusion			
Group A	22.9 ± 1.5*	1.8 ± 3.6*	51.2 ± 2.9
Group B	27.8 ± 2.9*	5.6 ± 6.0*	58.0 ± 3.2
Group C	16.3 ± 2.7*	12.6 ± 6.1*	41.3 ± 3.9*
3 hours' occlusion			
Group A	41.2 ± 4.0*†	29.4 ± 5.6*†	60.1 ± 4.2
Group B	31.9 ± 1.9*†	0.9 ± 5.7*	57.7 ± 4.4
Group C	10.0 ± 3.3*	4.1 ± 6.9*	52.7 ± 3.5*†

Values are mean ± standard error of mean. *, † $p < 0.05$ (* versus preocclusion, † versus 30 minutes of occlusion). Group descriptions as in Table

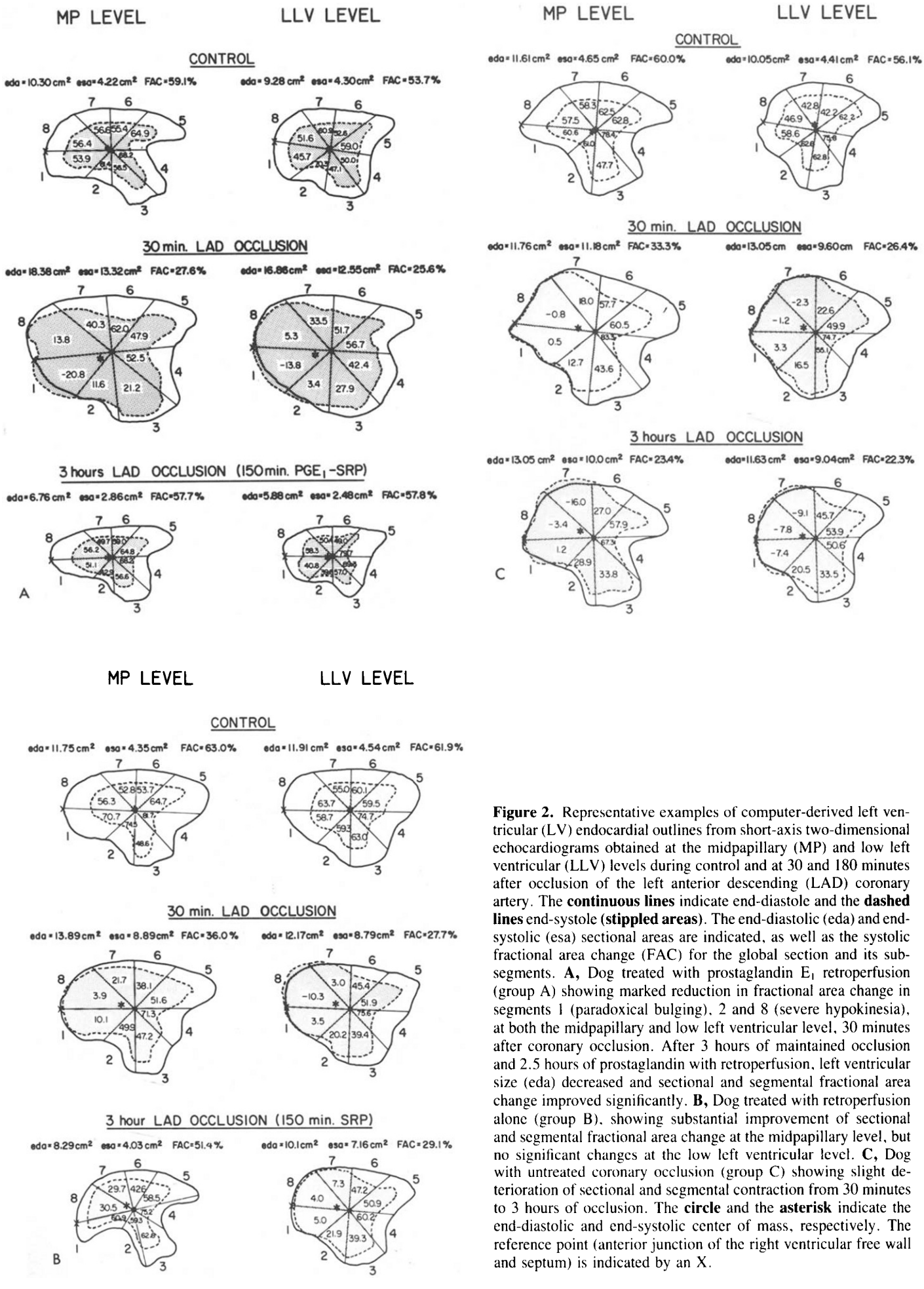

Figure 2. Representative examples of computer-derived left ventricular (LV) endocardial outlines from short-axis two-dimensional echocardiograms obtained at the midpapillary (MP) and low left ventricular (LLV) levels during control and at 30 and 180 minutes after occlusion of the left anterior descending (LAD) coronary artery. The **continuous lines** indicate end-diastole and the **dashed lines** end-systole (**stippled areas**). The end-diastolic (eda) and end-systolic (esa) sectional areas are indicated, as well as the systolic fractional area change (FAC) for the global section and its subsegments. **A,** Dog treated with prostaglandin E_1 retroperfusion (group A) showing marked reduction in fractional area change in segments 1 (paradoxical bulging), 2 and 8 (severe hypokinesia), at both the midpapillary and low left ventricular level, 30 minutes after coronary occlusion. After 3 hours of maintained occlusion and 2.5 hours of prostaglandin with retroperfusion, left ventricular size (eda) decreased and sectional and segmental fractional area change improved significantly. **B,** Dog treated with retroperfusion alone (group B), showing substantial improvement of sectional and segmental fractional area change at the midpapillary level, but no significant changes at the low left ventricular level. **C,** Dog with untreated coronary occlusion (group C) showing slight deterioration of sectional and segmental contraction from 30 minutes to 3 hours of occlusion. The **circle** and the **asterisk** indicate the end-diastolic and end-systolic center of mass, respectively. The reference point (anterior junction of the right ventricular free wall and septum) is indicated by an X.

Coronary occlusion was maintained in all 29 dogs for 3 hours. In the two treated series (groups A and B), retroperfusion was started immediately following measurements 30 minutes after coronary occlusion. In group A dogs, prostaglandin E_1 was infused continuously (25 to 30 ng/kg per min) into the retroperfusion line by means of a multispeed transmission pump (model 600, Harvard Apparatus Co.). Measurements were obtained in the preocclusion control period and at 30 and 180 minutes after the coronary occlusion.

Statistical analysis. Statistical analysis of the data consisted of a Kruskal-Wallis one-way analysis of variance. When this test indicated that a significant difference existed among the groups (probability [p] < 0.05), the Fisher's least significant difference test for multiple comparisons was used to determine which of the groups were significantly different from one another with alpha = 0.05. All of the tests are two-tailed. The results are presented as mean values and standard error of the mean.

Results

Hemodynamic effects of prostaglandin E_1 retroperfusion (Table 1). Because there were some differences in baseline hemodynamic values among groups A, B and C, only changes within each group were statistically analyzed. In all three groups of dogs, coronary artery occlusion caused an increase in heart rate and left ventricular end-diastolic pressure as well as in systemic vascular resistance, while maximal dP/dt and cardiac index decreased. Changes in systolic blood pressure were slight. Cardiac index decreased further up to the end of the experiments in groups B (retroperfusion alone) and C (no treatment), whereas dogs in group A (prostaglandin E_1 plus retroperfusion), the cardiac output was maintained after the prostaglandin retroperfusion treatment. Left ventricular end-diastolic pressure remained elevated up to 3 hours of coronary occlusion in group C (untreated dogs) but showed a dramatic decrease in both series treated with retroperfusion (groups A and B). A slight but statistically significant increase in maximal rate of rise of left ventricular pressure (dP/dt max) was noted in group A, appearing within minutes after the start of prostaglandin E_1 retroperfusion and persisting to the end of the experiments. In groups B and C, there was no significant change in dP/dt max between 30 minutes and 3 hours of coronary occlusion.

Electrocardiographic changes. All the dogs exhibited significant ST segment elevation after coronary occlusion. Ectopic ventricular activity was generally observed in the first 5 to 20 minutes after occlusion, and similar activity occasionally reappeared after close to 3 hours of occlusion in the untreated control dogs. In both treated groups, a trend toward electrical stabilization became apparent within 10 to 20 minutes after initiation of retroperfusion. Sinus tachycardia was observed in some dogs during the initial stage of the pulsatile treatment.

Echocardiographic analysis of left ventricular function (Table 2, Fig. 2). Coronary artery occlusion led to prompt and significant alterations in the echocardiographically derived index of segmental contraction, with severe hypokinesia or dyskinesia noted in zones subserved by the left anterior descending coronary artery, indicating profound regional myocardial ischemia. Thirty minutes after occlusion, echographic study at the low left ventricular level section indicated a significant reduction in anterolateral wall systolic fractional area change (from 53.0 ± 2.4 to 1.8 ± 3.6%, 53.3 ± 4.1 to 5.6 ± 6.0% and 54.3 ± 2.3 to 12.6 ± 6.1% in groups A, B and C, respectively). Smaller changes were observed in segments remote from the ischemic region. Whereas reduced contraction could also be demonstrated in short-axis cross sections at higher levels of the left ventricle, these changes were not nearly as profound as those at the midpapillary and low ventricular levels.

Further significant deterioration in ischemic zone contraction developed in the untreated control dogs (group C)

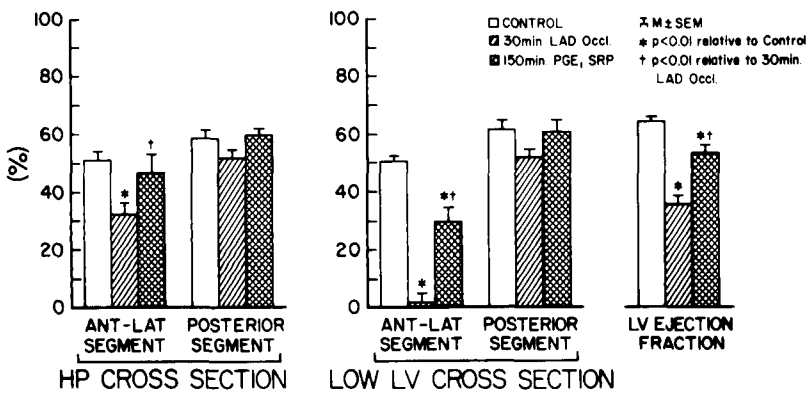

Figure 3. Effects of prostaglandin E_1 coronary venous retroperfusion (PGE_1-SRP) on left ventricular (LV) global and segmental function after left anterior descending (LAD) coronary artery occlusion (Occl.). Two-dimensional echocardiography was employed to derive systolic fractional area changes (FAC %) in high papillary (HP) and low left ventricular short-axis cross sections. ANT-LAT segment = anterolateral ischemic zone; M = mean; posterior segment = remote zone; SEM = standard error of mean.

Table 3. Myocardial Necrosis (N) as Estimated by Triphenyltetrazolium Chloride and Ischemia (I) (estimated by myocardial glycogen depletion in a mid-left ventricular slab) and as Percent of the Total Left Ventricular Mass

Dog	%I	%N	N% of I	N% of LV Mass
		Group A (prostaglandin E_1 retroperfusion)		
A-1	2.5 (P)	0	0	0
A-2	13.5 (C)	0	0	0
A-3	26.2 (C)	1.5 (P)	5.8	1.3
A-4	3.0 (P)	0	0	0
A-5	29.3 (C)	7.4 (P)	25.3	5.7
A-6	19.5 (C)	7.1 (P)	36.4	5.9
A-7	40.2 (P)	4.3 (P)	10.7	3.0
A-8	16.8 (C)	2.7 (P)	15.8	1.5
A-9	29.3 (C)	13.0 (P)	44.4	7.3
A-10	24.5 (C)	13.8 (C)	56.3	12.4
Mean	20.5	5.0	19.5	3.7
± SEM	± 3.8*	± 1.6*	± 6.4*	± 1.3*
		Group B (retroperfusion without drug)		
B-1	13.1 (P)	3.9 (P)	29.8	1.7
B-2	12.3 (P)	0.6 (P)	4.6	0.8
B-3	23.7 (C)	22.0 (C)	92.8	12.4
B-4	n/a	3.1 (P)	—	2.9
B-5	5.9 (P)	0	0	0
B-6	18.5 (C)	15.9 (P)	85.9	9.6
B-7	12.5 (P)	0	0	0
B-8	35.4 (C)	29.8 (C)	84.2	16.5
B-9	11.5 (P)	0	0	0
B-10	33.8 (P)	7.7 (P)	22.8	4.0
Mean	18.5	8.3	35.6	4.8
± SEM	± 3.5*	± 3.4*	± 13.5	± 1.9*
		Group C (occlusion without treatment)		
C-1	49.1 (C)	32.7 (C)	66.7	13.3
C-2	63.7 (C)	21.8 (C)	34.2	10.4
C-3	14.3 (C)	10.4 (C)	72.8	8.4
C-4	100.0 (C)	21.8 (C)	21.8	12.4
C-5	42.5 (C)	42.5 (C)	100.0	20.7
C-6	37.5 (C)	11.4 (C)	30.4	5.8
C-7	33.0 (C)	9.4 (C)	28.5	4.8
C-8	14.0 (P)	3.7 (P)	26.5	2.9
C-9	42.1 (C)	18.1 (C)	43.0	4.7
Mean	44.0	19.1	47.1	9.3
± SEM	± 8.7	± 4.1	± 8.9	± 1.9

* = $p < 0.05$ relative to Group C; C = confluent pattern; LV = left ventricular; n/a = not available; P = patchy pattern; SEM = standard error of the mean.

between 30 minutes and 3 hours of occlusion. During the same period of maintained coronary artery occlusion, retroperfusion with arterial blood only (group B) resulted in improvements in both sectional and ischemic segment contraction at the midpapillary section level. Thus, in the ischemic anterolateral region fractional area change increased significantly from 13.4 ± 3.9 to 32.1 ± 10.4% ($p < 0.05$), and in the remote posterior region from 53.0 ± 3.0 to 62.3 ± 2.9% ($p < 0.05$). Yet, at the low level section of the left ventricle where ischemic injury was most severe, retroperfusion alone failed to correct the profound anterolateral segmental dysfunction (Table 2).

In the prostaglandin E_1 retroperfusion group, improvements in both sectional and segmental contraction were evident at 3 hours of occlusion (Table 2, Fig. 3). Significant improvement in the anterolateral ischemic segment systolic fractional area change was observed even at the low left ventricular level (from 1.8 ± 3.6% at 30 minutes after occlusion to 29.4 ± 5.6% after 2½ hours of prostaglandin retroperfusion), although preocclusion levels of contraction were not reached. In the posterior ventricular wall segments, contraction which was slightly decreased at 30 minutes postocclusion returned to near preocclusion values. Corresponding improvements were demonstrated in global sectional

contraction and in left ventricular ejection fraction in group A, compared with no change or further deterioration in group C.

Myocardial infarct size and zone of ischemia (Table 3, Fig. 4). Compared with untreated control dogs (group C), dogs with prostaglandin E_1 retroperfusion (group A) exhibited significantly smaller infarct size after 3 hours of coronary occlusion (9.3 ± 1.9% of the left ventricle, versus 3.7 ± 1.3%, $p < 0.05$). Macroscopic examination of the stained ventricular slabs from the treated groups often revealed patchy and unevenly distributed subendocardial necrotic areas, predominantly at the apical and low papillary levels, whereas slabs obtained from untreated dogs with 3 hours of occlusion (group C) generally demonstrated widespread confluent infarcts. The ischemic glycogen-depleted area measured in a mid-left ventricular slice was also significantly smaller in size in group A than in group C (20.5 ± 3.8 versus 44.0 ± 8.7%, $p < 0.05$), suggesting a decrease in ischemia as a result of the prostaglandin E_1 retroperfusion treatment.

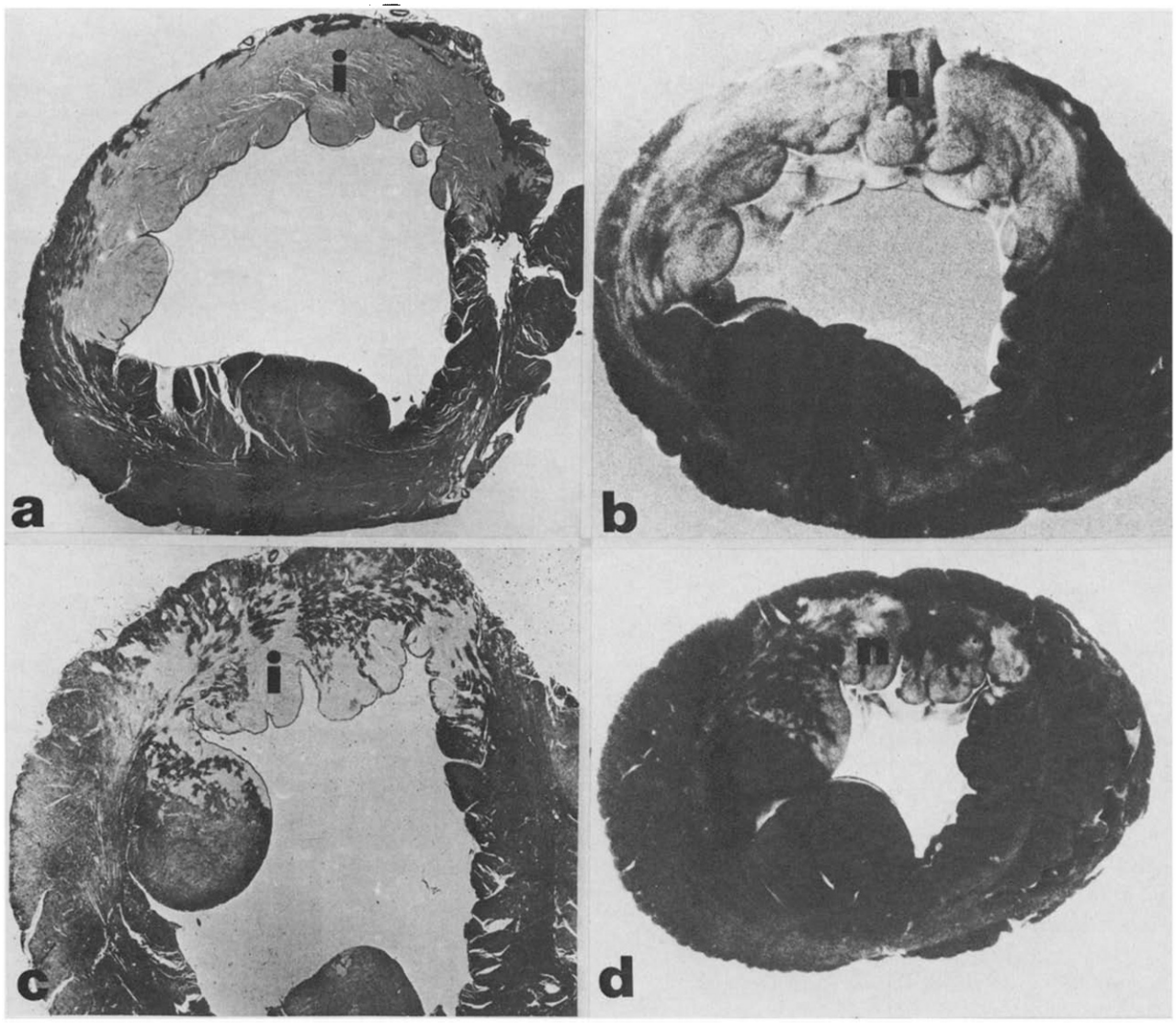

Figure 4. Examples of morphologic findings in dogs studied. **a,** Periodic acid-Schiff (PAS)-stained giant histologic section from a control dog (Group C, untreated 3 hour occlusion), showing a large confluent region of ischemia (i) as indicated by glycogen loss. **b,** Triphenyltetrazolium chloride stain of contiguous surface of adjacent slice of myocardium, showing a large confluent region of necrosis (n) (lack of staining). **c,** PAS-stained section from a dog treated with prostaglandin E_1 and coronary venous retroperfusion (group A). Glycogen loss (ischemia) (i) is less extensive than in the control dog and patchy. **d,** Triphenyltetrazolium chloride-stained contiguous surface of adjacent slice of myocardium showing a small patchy region of necrosis (n).

Discussion

Severe regional left ventricular dysfunction supervened very rapidly after proximal left anterior descending coronary artery occlusion in closed chest dogs. The jeopardized dys-

JACC Vol. 3, No. 4
April 1984:939–47

functioning zone was clearly delineated by two-dimensional echocardiography in short-axis cross sections of the ventricle, and this ischemic zone essentially corresponded to the extent of myocardial glycogen depletion outlined in equivalent slices of the heart (17). It is now widely appreciated that acute myocardial infarction generally develops as a result of a thrombotic coronary artery occlusion, and that in the absence of adequate preexisting collateral vessels, dysfunction sets in rapidly and regional myocardium at risk will be irreversibly damaged if it is not possible to institute an efficacious intervention. To be effective, such treatment must reach the jeopardized zone in sufficient measure and in time to ensure ischemic tissue survival.

Re-establishment of adequate coronary blood flow and myocardial perfusion. This is deemed the treatment of choice, and new nonsurgical and surgical reperfusion techniques are being applied. Yet, even when these newer treatments are used, pharmacologic support or circulatory assistance may be essential to maintain viability pending achievement of effective reperfusion (18). Unfortunately, access to the most profoundly ischemic segment of the heart distal to the coronary occlusion is frequently limited, so that direct beneficial effects of administration of pharmacologic agents may be minimal. The pulsatile coronary venous retroperfusion technique, previously examined by us and modified for the current study, represents an alternate mode of delivery of blood and agents to the endangered ischemic myocardium, along with potentially enhanced washout of metabolites. Although retroperfusion with arterial blood was shown to provide significant benefits, it has been the experience that the most distal myocardium beyond a left anterior descending coronary artery occlusion (near the left ventricular apex) may not be salvaged. We hypothesized that supplemental use of prostaglandin E_1 might enhance the retroperfusion performance and possibly provide salvage even in this most profoundly ischemic region.

Benefits of prostaglandin E_1 retroperfusion. Each of the three series of dogs in the present investigation (prostaglandin E_1 retroperfusion, retroperfusion alone and no treatment) developed severe ischemic dysfunction at 30 minutes after occlusion, following which the protocol called for differential treatment. In the dogs without treatment, function in the ischemic zone deteriorated further after up to 3 hours of occlusion, particularly in the profoundly injured anterolateral segments of lower ventricular cross sections, although contractile derangements were also seen at higher levels of the left ventricle. With 2½ hours of prostaglandin retroperfusion during maintained coronary occlusion, significant improvements were demonstrated by echocardiography even in the most profoundly ischemic area, and this was reflected in the significant reduction in infarct size compared with that in the untreated series, along with evidence of reduction in the extent of ischemia. Treatment with arterial blood retroperfusion alone during an equivalent period confirmed previous evidence of significant and prompt improvement of function and reduction of infarct size in most regions of the left ventricle, except in the most profoundly ischemic zone near the apex. Thus, prostaglandin supplementation was shown to provide additional benefits during acute myocardial ischemia in addition to those experienced with arterial blood retroperfusion alone.

Mechanism of prostaglandin E_1 retroperfusion. The action of prostaglandin E_1 delivered by retroperfusion into the ischemic zone may be associated with one or several of the reported direct myocardial mechanisms. Thus, prostaglandin-induced enhancement of myocardial contractility and reduction of preload (5,6,19) might be responsible for the observed improved ischemic zone contraction and lowered left ventricular end-diastolic pressure. Review of effects of prostaglandin E_1 on the coronary circulation suggests that this drug produces coronary vasodilation (3,20–22) as well as general relaxation of the vascular smooth muscle (23). Experimental data also indicate that prostaglandin E_1 might increase myocardial contractile force, reduce left ventricular end-diastolic length and increase cardiac output (3).

The effects of prostaglandin E_1 on the preservation of acutely ischemic myocardium have been studied in different species. Thus, when prostaglandin E_1 was administered intravenously in cats with coronary occlusion, there was a significant decrease in infarct size and improved hemodynamics were demonstrated (24). The mechanisms and effects of prostaglandins in various physiologic settings and myocardial ischemia remain controversial, presumably because investigators have used different species, different protocols and a wide range of drug dosages. Nevertheless, prostaglandin E_1 seems to have a general beneficial action in acute myocardial ischemia. The apparent ability of the drug to improve myocardial perfusion through coronary vasodilation and its beneficial hemodynamic effects have stimulated initial clinical trials in patients with unstable angina pectoris and acute myocardial infarction (19).

Clinical implications. The clinical potentials indicated by this study transcend the use of prostaglandin E_1 retroperfusion. Our evidence suggests that synchronized coronary venous retroperfusion may effectively deliver drugs to the acutely ischemic myocardium for maintenance of its function and viability. A series of pharmacologic agents previously considered beneficial in the setting of acute ischemia, particularly those with direct myocardial effects, should now be re-examined with more appropriate coronary venous delivery and consequently enhanced local drug concentration.

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